A CLINICAL EVALUATION OF ANTIHYPERTENSIVE DRUGS*

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THE past ten years have seen the transition from an era of almost drugless therapy of arterial hypertension to one which baffles the clinician with its multiplicity of drugs. It is good now and again to stop amid the claims and counterclaims and take stock of what has been accomplished and what needs doing. Maybe there are so many drugs now available because, like women's hats, no one likes to make the same mistake twice.

GOALS OF ANTIHYPERTENSIVE DRUG THERAPY

First let us look at what we are trying to do. As I see it, we want 1) to reduce arterial pressure to as near normal levels as possible except in advanced arteriosclerotic hypertension; 2) to induce few side effects; 3) to prevent the cardiovascular disease which usually accompanies hypertension; 4) to prolong life and to make it more pleasant and comfortable; 5) to keep expenses reasonable.

How far along are we in our search for these desirable objectives? I should think not very far, yet the first vital step has been taken and investigators and clinicians alike are alert to the need of antihypertensive drug therapy. The old Cohnheim conception that blood pressure is elevated to insure adequate perfusion of tissues seems to have died a quiet death, which is just as well. At last the drug manufacturers are also working hard on the problem and now constitute the chief source—usually the only source—of experimental drugs. It is puzzling that manufacturers were so slow in taking up the problem, but now, once under way, their program is proving quite effective. Much the same turn of events is now occurring in the fields of atherosclerosis and neurochemistry.

* Presented at the 29th Annual Graduate Fortnight of The New York Academy of Medicine, October 17, 1956.

Can arterial pressure be reduced satisfyingly by the drugs now available? I estimate that this is possible in about half the patients. The other half is anything but satisfying. There usually are temporary falls in arterial pressure with each new drug used but the falls do not last and another drug is tried with much the same lack of success. This fact proves beyond doubt that we are far from our goal of adequate blood pressure reduction.

Side effects are so common with all of the drugs now available that they are almost taken for granted. One has only to think of the parasympathetic effects of ganglion blocking agents to realize how much we have had to accept as the price for lowering blood pressure.

We have pointed out[1] after 26 years of trying to treat hypertension, that, while ability to lower blood pressure has improved, the prevention and treatment of the accompanying cardiovascular disease has advanced little. It is true that most evidence now strongly suggests that heart and blood vessel disease is less likely to occur when blood pressure is held within normal limits; consequently, what progress has been made has been the result of keeping the blood pressure down. The contrary view that the vascular disease precedes the hypertension has received little support recently. But until we know more about the treatment of the vascular disease and especially that in the cerebral, cardiac and renal areas, the problem of treatment of arterial hypertension will not have been solved. It is a complicated and difficult one but its pervading importance must nudge us into greater effort.

Whether, as physicians, we have made life richer and more comfortable as a result of drug therapy is a problem I approach with some misgivings. I am certain that we have all made some patients miserable. But, on balance, I would guess that the net effort has been for the better. Without being able to prove it, I believe that many patients' lives have been usefully prolonged. Of one thing I am certain, and that is that the vascular changes of malignant hypertension can be reversed, a phenomenon I saw for the first time following anterior spinal nerve root section. For those of you who are young, this was the operation devised by Adson which preceded the more modern sympathetic ganglionectomy such as that of Smithwick.

Currently we are in a highly experimental phase in the use of antihypertensive drugs. All sorts of chemicals are under test in the hope that they will prove useful. This does not make it easy for our

patients but I see no way, after animal tests are completed, of avoiding the crucial test on the hypertensive patient.

It is the side effects of the antihypertensive drugs in most cases which cause the discomfort. These miseries are no strangers to you, a group of practicing physicians, and I will not insult your experience by recounting them. I would like to point out that there is a growing list of syndromes, some of them fascinating, which are iatrogenic, but which when their mechanisms are understood, will give important understanding of disease of the most varied nature. I refer, for example, to hydralazine disease, which elicits both a rheumatoid arthritis-like state and a lupus erythematosus-like one.

To some degree comfort and expense go hand in hand. Hypertension is a chronic state often lasting several decades. For this reason alone, the cost of the drugs prescribed should receive consideration. Some will say this is not the province of the physician. I disagree. Finance is one of the important stresses and strains to which the hypertensive is subjected. It is often at the very heart of the mechanisms of hypertension. Every effort must be made by manufacturers to price their products reasonably, to reduce advertising costs to a minimum and provide as much stability in the market as is consistent with advance in knowledge. As more and more chronic diseases such as hypertension and arteriosclerosis are being added to the list of those possibly amenable to drug therapy, the financial problem becomes progressively more urgent.

Difficulties of Objective Evaluation of Drug Action

One fact always puzzles the newcomer in the field of hypertension. How can there be such a variety of results and interpretations when a given drug is used in the same type of patients by different investigators? Let's be very personal and take examples from the current literature written by competent observers about the same drug, reserpine. Bello and Turner[2] find ". . . the drug had no significant effect on pulse or blood pressure." But listen to Smith and his associates.[3] "Sixty-three percent of the patients had become normotensive by the conclusion of the study." Appearing in the same journal and within a short time of each other, the reader must be left wondering. The same type of illustration is found in the problem of toxicity with some observers finding none and others describing the most alarming reactions. This

confusion is not limited to the Rauwolfia drugs. As nearly as I can discern, the English clinicians in general think very poorly of hydralazine (Apresoline) while in this country, Germany, Denmark and Sweden, it seems to have become established as a useful drug once its idiosyncrasies were understood. It is an almost black and white contrast.

I don't want to belabor the point because I think most clinicians are aware of both the confusion in the literature and how badly it is in need of having the white of an egg dropped into it. I shall be content to stress only three more points.

1. The therapeutic effectiveness of a drug appears to depend on its ability to lower arterial pressure sufficiently to prevent the progress of vascular disease and relieve the load on the heart. One often reads that such and such a drug lowers blood pressure "significantly" but the reader is not informed what the author considers "significant" from a practical clinical point of view. I mean by "significant" what I have just said. Even the question of the validity of a cause and effect relationship between treatment given and the effect on blood pressure periodically comes under fire. A particularly devastating examination of the problem has recently been published by Goldring, Chasis, Schreiner and Smith.[4] Intensive reassurance with the aid of an "atom gun" brought an average decrease of 38/28 mm. Hg which is considerably better than some of the "significant" falls recorded for some drugs. But even this type of study depends much on the kind of controls that were used.

2. The second point is one that always seems to arouse my diencephalic centers with perhaps some associated cortical inhibition. It is the view that arterial hypertension is a unitary disease. I am sure most realize this is not true, but often they don't act as though they do. Why would it be expected that a drug which acts primarily on one mechanism, would reduce pressure with any degree of specificity if an entirely different mechanism were involved. If, for example, the nervous system were blocked off by hexamethonium, moderate fall in blood pressure would occur even if the nervous system were just doing its normal task and not involved in the mechanism of the hypertension. If the hypertension were being maintained by some renal factor, the loss of nervous tone would not be expected to abolish it.

3. There seems to be a growing tendency to believe that the larger the series the greater the accuracy of the results. Instead of studying 10 or 50 cases thoroughly, hundreds or thousands now seem

to be necessary to carry conviction. I am baffled by the casual bandying of the 300 to 3000 patients who were studied personally by one man. The simplest reflection shows that such a study could only be superficial in the extreme; a few scattered blood pressure readings in an office, often spaced months or years apart, administration of a drug and more scattered pressure measurements. These data become a figure in a printed column spelling success or failure of treatment. I submit that this sort of study may be worse than useless because it can so often be misleading. I remember one day trying to flatter your and my old and respected friend, Dr. Alfred Cohn, while we were seeing a patient with coarctation of the aorta. I said I knew from the many cases he had seen that this one had nothing new for him. He replied that he had seen innumerable patients with coarctation but had studied two. Like Dr. Cohn, I find myself singularly unimpressed by "bulk method" of studying hypertensives.

These are only some of the facts illustrating why there is not more unanimity about the value of particular drugs in the treatment of arterial hypertension. Until we know more about the specific mechanisms involved, it is unlikely the situation will improve very much. There are few fields in which so many leads have been opened for investigation and so few of them being followed up. Despite the great demand for, and sale of, antihypertensive drugs, fundamental research on the nature of hypertension is altogether inadequate.

Common Sense and Its Congeners

We are in an era when a pill is often substituted for common sense advice. This is much more apt to be effective in acute than in chronic disease. Patients have to learn to live with themselves and with their disease. The union can be a happy and productive one, depending often upon the pre-marital instruction.

The best initial approach to the patient seems to me to be an educational one; to face the problem of the disease with the patient and to lead him away from fear by teaching him wherein his fear arises. Certainly, infinite patience is required to listen to the initial history of a garrulous woman, what someone has called, "the preamble to her constitution." We use discussion and reading material but I must confess that I don't think we do nearly a good enough job. I have tried to be helpful by writing a manual for hypertension patients which seems,

for reasons entirely unclear to me, to have received more acceptance by physicians than by patients: it has had little impact on the big problem. There is great room for group or class room demonstration and teaching. Rehabilitation, both mental and physical, is a pressing demand with such catastrophes as stroke being such a common cause of morbidity. I wish we did as well in our field as is done by many of the diabetic clinics.

In sum, it would be a pity if we substituted pills for the human warmth and understanding a physician owes his sick patient. The latter are particularly necessary when dealing with chronic diseases. Nor must there be erected too many "don'ts" as road blocks to happiness. Remember, for a good life, be moderate in all things, but don't miss anything. This is my only real "don't."

It is perhaps presumptuous on my part to stress another facet of common sense in the treatment of hypertension. I do it because I hope all of us will be constantly on the alert to better our methods of diagnosis. Little by little small groups of patients with unitary mechanisms are being chipped off of what has appeared to be a monolith. These people often turn out to have correctable defects. I think, for instance, of those we have been uncovering at the Cleveland Clinic where the aortogram has shown defects in the renal vessels correctable by arterial transplants. The urologist and vascular surgeon can make an important therapeutic contribution to this small group of patients.

The time cannot be far off when some creative investigator will find chemical ways of making the correct mechanistic diagnosis and then I am sure that much of the current haze in treatment will be dispelled.

Ganglion Blocking Agents

These substances act by competing for acetylcholine which is the transmitter of nerve impulses passing through autonomic ganglia. While there may be other transmitter substances in ganglia, none are currently recognized.

Except for one, mecamylamine, studied by Freis and Wilson,[5] Moyer and associates[6] and others, all the ganglioplegic agents in current clinical use are quaternary ammonium derivatives. Their chemical structures are similar to that of acetylcholine and they compete with it for receptor sites. Since both sympathetic and parasympathetic ganglia have

the same transmission mechanisms, both become blocked by these agents. I need hardly tell a sophisticated audience like this that herein lies a serious difficulty with these agents.

You are all sufficiently familiar with the actions of these substances not to need me to review them for you. There is still some uncertainty as to the precise physiological mechanisms involved in the lowering of arterial pressure. Probably those[6a] who believe in reduced venous return with reduced cardiac output have somewhat the edge over those[6b, c] who believe more in arteriolar dilatation with reduced peripheral resistance as the prime cause. The two points of view by no means seem to be exclusive and which is the more ascendant may well depend on the state and position of the patient. As an example of what I mean, some patients exhibit clear hypotensive responses when pressure is measured in the supine position; many do not. When those of the latter group stand up their pressures fall sharply and remain lowered. Still others only show a marked hypotensive response when they exercise. Here are the blood pressure measurements of such a patient:

	Supine	Standing	5 minutes walking
Average	210/30	157/109	124/91 mm. Hg

When the patient sat upright on a stationary bicycle and pumped his legs, arterial pressure fell from 142/103 to 122/78 mm. Hg. If, on the contrary, he lay prone and lifted 3 pound weights on each foot blood pressure also fell (194/127 to 162/100). Clearly then, exercise hypotension following ganglioplegics is not necessarily a result of posture, a fact not generally recognized.

The fall in cardiac output with decreased venous return and pooling or trapping of blood theoretically would not be the best way to reduce blood pressure in patients with increased peripheral resistance and normal cardiac output (Crosley and associates[7]). But so far no one has shown that such chronic trapping of blood is harmful. Perhaps fortunately in the kidneys there occurs some decrease in calculated vascular resistance (Del Greco, Corcoran and Page[8]).

With the appearance of each new ganglion blocking agent since hexamethonium, there has been a wave of advertising enthusiasm followed by almost as enthusiastic clinical reports, both of which quietly are forgotten when still another agent appears. In retrospect, it is hard to see that major improvements have been made except for improvement in absorbability. For what they are worth, here are my opinions,

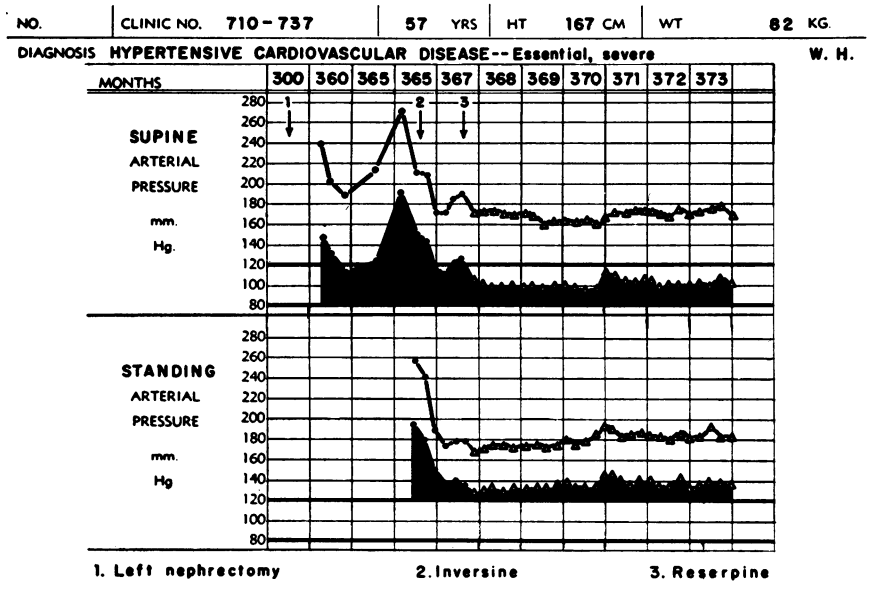

Figure 1.—Example of the effectiveness of mecamylamine in a patient with severe essential hypertension. Each dot on this and succeeding charts represents the average of four daily blood pressures for one week; the vertical divisions separate periods of one month. In this patient the drug elicited lowering in both the supine and standing arterial pressure. The addition of reserpine lowered slightly the dosage of mecamylamine required.

which have to remain opinions until more objective evidence is forthcoming. The absorbability of the drugs has been greatly improved, consequently the danger of irregular absorption seems no longer to exist. The sheer bulk of drug to be swallowed has been reduced. Side effects resulting from parasympathetic blockade are still with us and unabated. Refractoriness appears in some patients with all agents. Whether the length of time of action has been increased is hard to answer; and so far, bear in mind, that no one has presented objective evidence on this point. Our impression is that no great change has been effected. One thing is certain and that is the price has gone up.

Let me summarize briefly our relatively extensive experience with two of the latest substances, mecamylamine (Inversine) and Chlorisondamine (Ecolid). Mecamylamine is unusual in that it is a secondary amine and not a quaternary ammonium compound. It seems to be absorbed completely from the gastrointestinal tract. Schneckloth, Corcoran, Dustan and I[9] found it effective in about one-half of hypertensives given an average dose of 25 mg. It is no more effective in

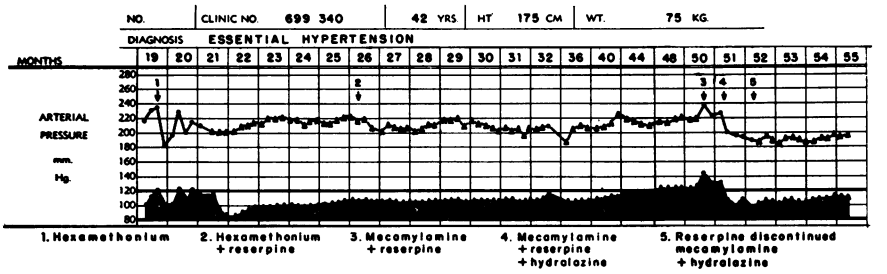

Figure 2.—Gradual loss of response to the ganglion blocking agents hexamethonium and mecamylamine (1-3). Reserpine had little effect (2). Addition of hydralazine again gave a fall in blood pressure (4). Discontinuing reserpine caused no rise in pressure. This illustrates the need for constant supervision of treatment and the search for effectiveness of each drug.

lowering arterial pressure than other ganglion blocking agents and the needed dose from day to day is also variable. This variability can be very disturbing as it is usually entirely unpredictable. Patients are on the whole more sensitive in the morning than in the evening and possibly more so if they are bed-fast. Side effects resulting from parasympathetic paralysis are similar. Constipation often needs to be prevented by diet, cascara or magnesium oxide. At times neostigmine needs to be given to secure a bowel movement. Dryness of the mouth may be combated with 5 to 10 mg. of pilocarpine taken orally about a half hour before meals. The therapeutic advantage lies mainly in the predictability of intestinal absorption and the ease of handling patients on this drug. Contrary to some claims, when refractoriness is induced by other ganglioplegics, response to mecamylamine is also lost in both man and animals.

A neuromuscular disorder has been observed in some of our patients. It manifests itself as anxiety associated with jerky, choreiform movements and tremor, especially of the hands and arms. Bizarre mental aberrations occur and two of our patients had convulsions. Remission occurs on discontinuing the drug. Diffuse hypertensive cerebro- and/or renal vascular damage seems to provide the favorable substrate on which this syndrome makes its appearance. Renal failure is not a necessary accompaniment. Possibly some degradation product of mecamylamine causes the nervous excitation in these few patients, especially since the camphane nucleus may be associated in derivatives with excitatory properties. Knowing of this syndrome we do not believe it constitutes a serious handicap to the use of the drug.

Ecolid is a good blocking agent with regular absorption (Plummer and associates[10]) studied clinically originally by Grimson and Winsor. Its dosage is small, average maintenance being 50 to 100 mg. b.i.d. So far we have seen no complications as the result of its use but we must remember that hexamethonium was used much more extensively before the hexamethonium lung disease appeared. Patients are relatively easy to handle when Ecolid is used. We use it in our severe and malignant hypertensives and only occasionally in those with the more moderate variety.

Both mecamylamine and Ecolid exhibit the usual beneficial effects on the decompensated hypertensive. With a fall in pressure compensation often appears without use of digitalis.

I don't wish to sound negativistic but I think it better to point out some of the difficulties that you as physicians are going to face in the daily use of these drugs. Clearly, they are a useful addition in the treatment of some types of hypertension, but they have serious limitations and these must be recognized lest a wave of nihilism engulf their use completely. This has happened to other drugs. We owe much to Smirk of New Zealand for the skill and conviction with which he demonstrated how to use these drugs and to Paton for their introduction.

Much more needs yet to be done to understand why the ganglion blocking agents fail in so many cases, why refractoriness develops and why supine pressure is often so little affected. We have not yet learned how to exploit "exercise hypotension." I cannot feel content to count the limited blessings of ganglioplegics without a very uneasy glance at their side effects and the long term results of widespread ganglion blockade.

Reserpine

The problems of reserpine have been so adequately described (Vakil[11]; Wilkins[12]), I think I can safely pass over it with a few notions about its use in hypertensives. I have already pointed out there are still those who find it has no effect on blood pressure and others that it lowers pressure "significantly" in some 70 per cent of patients.

We have convinced ourselves that reserpine in doses of about 0.25 to 1 milligram exhibits the same variability of effect as all other antihypertensive drugs. Nor are we able to predict which patients will show a good hypotensive response. It is purely trial and error just as is dosage. Despite all of the words used so far to describe the cerebral pharmacology of this drug, what information there is has been of little

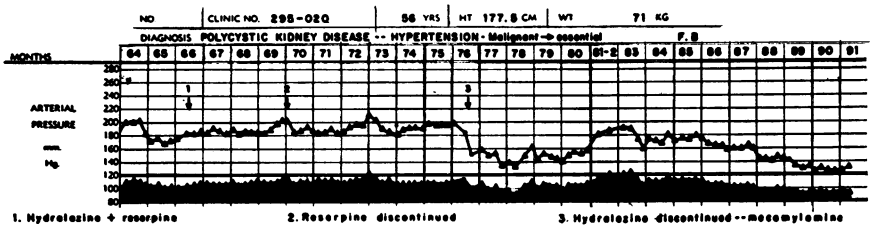

Figure 3.—Failure of hydralazine and reserpine to control blood pressure adequately but successful use of mecamylamine. At (3) mecamylamine was started.

use in treatment of patients. The drug has a very prolonged action yet isotope studies show it to be rapidly metabolized; 30-40% appears in the urine as trimethoxybenzoic acid within four hours.

Combining reserpine with other drugs such as Ecolid or mecamylamine allows reduction of the dose of the ganglion blocking agent in some patients. In others, combined therapy is completely ineffective.

Occasionally the drug has seemed helpful in preventing the tachycardia, headache, flushing, etc., which may result in the first few weeks of administration of hydralazine. But again there is no regularity in this action.

Although reserpine is believed to be completely and regularly absorbed by mouth, we have given it intramuscularly to see if the effects differed. When 1 mg. is given in this way blood pressure may be profoundly lowered while, given by mouth the hypotensive effects may be small. But single parenteral administration gives no clue as to whether chronic administration by mouth will effectively lower arterial pressure. We have no reasonable explanation for this observation.

Brodie and his group have presented strong evidence suggesting that reserpine acts by liberating serotonin from the brain, which is then destroyed by amine oxidase. Shaw and Woolley[13] have prepared a large group of serotonin competitors one or two of which are said by Wilkins[14] to have an antihypertensive and reserpine-like action. This is an interesting line of thought and one well worth investigating.

Considering the amount of reserpine currently consumed, the number of toxic side effects must be small. On the other hand, some take an entirely too optimistic point of view. Everyone who has used reserpine has seen severe drowsiness, serious mental depressions, parkinsonism and other more minor disturbances (Freis[15]). These should be watched for and should not be dismissed lightly. The thought that these

drugs should be used for "nervousness", "tension", and all manner of ill-defined states, without careful attention of a physician seems to me nonsense. We have no experience with Feinblatt's[16] suggestion that 8 mg. of ephedrine combined with 0.1 to 0.2 mg. of reserpine relieves most of the side effects.

Reserpine can be valuable in the most varied types of hypertension. Wilkins suggested its use in the very early cases and yet Robert Platt finds it useful in malignant hypertension; a more diverse substrate could hardly be imagined.

Tranquilizing agents other than reserpine have not been used by us to any large extent. We have tried a combination of chlorpromazine with mecamylamine or Ecolid with no striking success. The effect seems purely additive. Patients with severe cerebrovascular disease and mental disturbance have definitely been benefited by chlorpromazine as have some with uremia.

Hydralazine (Apresoline)

This drug has now been widely used for about six years, yet there is still much disagreement about its value. Such able clinicians as McMichael, Smirk and Moyer find it of little use. This has not been our experience nor that of many others. In about one quarter of our patients blood pressure was reduced to normal and in another quarter diastolic pressure was reduced to 100-110 mm. Hg when this drug was used alone. The patients all had severe hypertension. I have no explanation for the failure of others to have at least some good results except possibly the care and persistence with which it is given in our Clinic. Almost all of our patients have had long periods in the hospital where new drugs are being studied and I suspect this accounts for much of the diversity of the results when compared with patients given drugs as out-patients. Most of our patients measure their own blood pressures when they are at home.

The initial side effects of Apresoline often discourage patient and physician alike from continuing with the drug. They may last for as long as eight weeks. During this period reserpine and/or antihistaminics are at times of value in preventing or lessening some of the side effects and allowing the dosage of Apresoline to be raised to between 600 and 800 mg. in a shorter time. After the maximum dosage and response have been attained we reduce maintenance dosage to between 300 and

400 mg.

We[17] with Schroeder[18] described in a few patients a fascinating new syndrome associated with administration of large doses of Apresoline. One part of the syndrome resembles early rheumatoid arthritis and the later and severer form acute systemic lupus erythematosus. The condition is reversible. To me its greatest interest and importance lies in the fact that experimentally a known chemical agent has produced a collagen disease for the first time. Comens,[19] in Schroeder's laboratory, has elicited a lupus-like syndrome in dogs fed Apresoline for four months. Curiously, others seem unable to get the same results. While these observations are of the greatest interest from the point of view of theory of collagen diseases, too much should not be made of them from the practical clinical viewpoint. The physician aware of the syndrome is forewarned and may avoid it altogether.

Schroeder, Morrow and Perry[20] in particular, have been strong advocates of combining Apresoline with hexamethonium, finding a synergistic action between the two drugs and an extraordinarily high percentage of success with the treatment. Others have confirmed and denied these claims. We have not been able to convince ourselves that any true synergism exists either from laboratory experiments or from bedside observation. Some of our patients have done better on combined treatment than on each drug alone. We continue to believe that some patients do not respond satisfactorily to one or the other drug and that combining this agent with another does not improve the response. But when each alone is shown to be useful, then a combination may be more successful. We have been accused of opposing combinations of drugs and this is true to the extent that we do not believe drugs should be given when their usefulness in an individual patient is unproved. So many hypertensives, for reasons entirely unknown, fail to respond to one or another drug. We have also vigorously opposed sale of combinations of drugs which make dosage regulation of the individual drugs impossible.

Six years' experience (Taylor, Corcoran, Dustan and Page[21]) with Apresoline leaves us convinced that, when used carefully and with cautious persistence, it is a valuable antihypertensive drug compared with others currently available. It often may be used successfully in combination with other measures. As a treatment, like all other antihypertensive treatments, it leaves much to be desired.

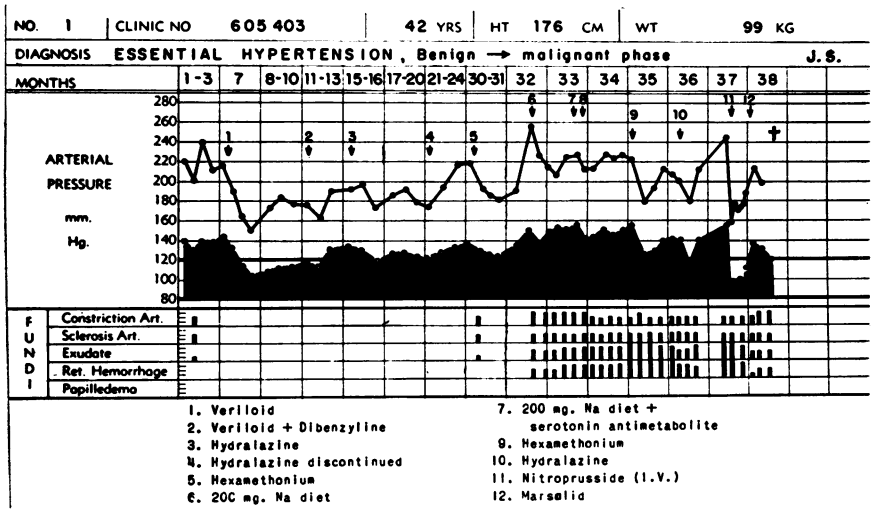

Figure 4.—Failure of a variety of antihypertensive agents to control blood pressure in a hospitalized patient. The following measures were tried:

1. Veriloid
2. Veriloid + Dibenzyline
3. Hydralazine
4. Hydralazine discontinued
5. Hexamethonium
6. 200 mg. Na diet
7. 200 mg. Na diet + serotonin antimetabolite
9. Hexamethonium
10. Hydralazine
11. Nitroprusside (I. V.)
12. Marsalid

Failures

Failures of treatment are an unpopular subject for discussion (as I have found[22]) yet to me what is behind failure may give the clue to success. Since about one-half of the severe hypertensives fail to respond satisfactorily for one reason or another, a great deal of attention should be given to these partial, or complete, failures. It is much pleasanter to recount one's successes but I shall be the devil's advocate and for the time being "raise the devil" to emphasize this aspect of current practice. As my first dart I think it fair to say that if you have no failures in your practice you will not recognize your true successes either. In short, study of your patients is inadequate.

Let me give you an example of one of our failures, a patient who spent most of his days under study in our hospital with almost nothing to show for it—not even a bill. His response to everything we tried was inadequate; intravenous infusion of sodium nitroprusside was the only measure that kept his arterial pressure down. Reserpine was not available at the time so he had no trial of this drug. It seems to me profitable to examine this chart carefully.

Failures are mostly of four sorts: 1) despite rigid adherence to treatment no response occurs to any of the measures employed; 2) the response is good but transient; 3) the response is poor but the reasons for it are clear; the patient takes treatment only when the spirit moves him and evidently the spirit is weak; 4) the side effects of the drugs are too disabling.

This always brings me to the point that until we know more of the mechanisms which are keeping the arterial pressure up, any thought of specific treatment is out of the question. We shall continue our groping empiricism until renal, neurogenic, cardiogenic and endocrinogenic hypertension become more than just words.[23] The uncovering of mechanisms in hypertension has failed to fire the imagination of scientists for the most part, hence progress is painfully slow. Correspondingly, too great optimism in our appraisal of treatment will only put off the day when treatment will be tailored to underlying mechanisms. Not to make an invidious comparison, but I doubt that "hot leads" in the field of cancer would receive such parsimonious interest as in the field of hypertension.

The Coming Era of Arteriosclerosis

Perhaps one of the most cogent arguments in favor of the view that antihypertensive drugs are prolonging patients' lives is the appearance of more and more vascular diseases. In the past few years we have been greatly impressed by the numbers of our patients treated for long periods who now show advanced arteriosclerosis, especially of the cerebral vessels.[24] More and more behavioral problems and frankly psychotic episodes are troubling us. Autopsy reveals widespread and severe atherosclerosis.

The manifestations of thrombosis and hemorrhage seem to come in attacks constituted of several strokes in the course of a few weeks interspersed with days of psychotic behavior or long periods of semiconsciousness. As Dr. Dustan expresses it, "the patients seem to be coming apart at the seams."

We are very much puzzled to know the cause for the extreme severity of the atherosclerosis. While we cannot prove it, the era now upon us seems quite different from that of ten years ago, due, I think, to the prolongation of life of the hypertensive by lowering his arterial pressure without correspondingly effective treatment of the vascular disease.

Conclusions

I hope my remarks on the treatment of hypertension will not be taken as nihilistic, because as many of you know, I am a chronic optimist. I would have to be to have stayed in this field for 26 years. Success in many aspects has been phenomenal, especially when one realizes that we started with some first rate misconceptions, no good experimental methods and no treatments worthy of the name.

Treatment today is comparable to the treatment of diabetes 30 years ago. It requires endless patience and far more time than most patients or physicians are willing to give. It is not a disease easy to treat and it is becoming more difficult to treat well as time goes on.

Enough patients with severe hypertensive disease are now being kept alive so that clinical manifestations of the associated vascular disease are looming larger and larger. Certainly 15 years ago we did not see the bizarre mental and morphological disturbances we are now seeing due, chiefly, to keeping patients alive so much longer. Cerebrovascular disease is becoming quite as important to treat as it is to lower blood pressure. A new spate of problems is upon us and a fresh approach needs to be taken. But let me emphasize again that while we all feel overwhelmed by new problems, the old ones are still far from satisfyingly solved. We still need better methods to lower blood pressure and to keep it down. We still must find out why we fail so often. We still must find the mechanisms causing the elevated blood pressure. We have not been able to buy success cheaply and we must not count on it in the future. Let us keep clearly in view the successes but also the failures which constitute the fabric of progress through research.

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